Rebuttal from L. F. Barros and B. Weber

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Abstract: Comment on CrossTalk opposing view: lack of evidence supporting an astrocyte-to-neuron lactate shuttle coupling neuronal activity to glucose utilisation in the brain. [J Physiol. 2018]

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CROSSTALK

Rebuttal from L. F. Barros and B. Weber

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Bak and Walls (2018) chose two specific aspects of brain metabolism: the usage of glucose by neurons and the differential expression of monocarboxylate transporters (MCTs) and lactate dehydrogenase (LDH) isoforms. We do not have strong objections to their more general claims.

The astrocyte-to-neuron lactate shuttle (ANLS) – right from the get-go – has not disputed neuronal glucose metabolism. We concur with our colleagues in that neurons have glucose transporters and that they metabolise glucose, as shown in NMDA-stimulated neurons in culture (Bak *et al.* 2009), and as reported by many others in diverse preparations. It is also well established that neurons have a conspicuously active Ca^{2+}-dependent malate–aspartate shuttle (Llorente-Folch *et al.* 2013), and are therefore well equipped to metabolise glucose and lactate at the same time during activity. The critical question about neuronal glucose consumption is not qualitative but quantitative. What we do not agree with is that there is preferential consumption of glucose by neurons as concluded by Patel *et al.* (2014) and Lundgaard *et al.* (2015). In our opinion, these two studies should be interpreted with caution for technical reasons that were advanced in our CrossTalk article.

We also agree with Bak and Walls (2018) in that differential expressions of MCTs and LDH in neurons and astrocytes do not demonstrate vectorial flux because the direction of flux is not governed by kinetics but by gradients. Indeed, compelling support for ANLS comes from the finding of steep astrocyte-to-neuron gradients for lactate in the somatosensory cortex of anaesthetised mice (Machler *et al.* 2016), and for NADH/NAD^+ in mouse hippocampal slices (Mongeon *et al.* 2016), the latter likely to remain steep during neuronal activity (Diaz-Garcia *et al.* 2017). In addition to these gradients the astrocytic membrane potential acts as a driving force, which extrudes lactate through ion channels (Sotelo-Hitschfeld *et al.* 2015; Karagiannis *et al.* 2016). Thus, the consumption of astrocytic lactate by neurons is not only favoured kinetically but also thermodynamically.

Beyond doubt anaesthesia affects metabolism, a caveat that also applies to non-physiological conditions prevalent during cell culture and tissue culture work. For these reasons, no single piece of data may be taken as definitive proof of ANLS. And it is true that many experimental findings should be replicated in awake behaving animals. What presently makes ANLS a strong hypothesis is the convergence of experimental evidence acquired by many groups using various models under diverse experimental conditions.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have contributed to the conception or design of the work, acquisition or analysis or interpretation of data for the work, and drafting the work or revising it critically for important intellectual content. Both authors have approved

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the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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